Amendments to the Drawings:

The replacement drawing sheets attached in connection with the above-identified application containing FIG. 1, FIG. 2, FIG. 3, FIG. 4A, FIG. 4B, FIG. 4C, FIG. 5, FIG. 6A, FIG. 6B, FIG. 6C, FIG. 7A, FIG. 7B, FIG. 8, FIG. 9A, FIG. 9B, FIG. 9C, FIG. 9D, FIG. 10A, FIG. 10B, FIG. 11A, FIG. 11B, FIG. 12A, FIG. 12B, FIG. 13A, FIG. 13B, FIG. 14A, FIG. 14B, FIG. 14C, FIG. 15A, FIG. 15B, FIG. 15C, FIG. 15D, FIG. 16A, FIG. 16B, FIG. 17A, FIG. 17B, FIG. 17C, FIG. 17 D, FIG. 19A, FIG. 19B, FIG. 19C, FIG. 19D, FIG. 19E, FIG. 19F, FIG. 19G, FIG. 19H, FIG. 19I, FIG. 19J, FIG. 20A, FIG. 20B, FIG. 20C, FIG. 20D, FIG. 20E, FIG. 20F, and FIG. 21 are being presented as new formal drawing sheets to be substituted for the previously-submitted drawing sheets. The drawing figures have been amended to individually label each panel and increase the size of the lettering. No new matter has been added.

REMARKS

By the present communication, claim 1 is amended and claims 14 and 163 have been cancelled without prejudice. Claims 9 and 11 are withdrawn from consideration. Applicants reserve the right to pursue the subject matter of the cancelled claims in one or more timely-filed continuation or divisional applications. Upon entry of the present amendment, claims 1-4, 6-8, 10, 13, 27-37, and 168-172 will be pending and under examination. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Drawings

Replacement drawing sheets are being presented as new formal drawing sheets to be substituted for the previously-submitted drawing sheets. The drawing figures have been amended to individually label each panel and increase the size of the lettering. The photographic images are of highest obtainable quality. No new matter has been added. Applicants respectfully request withdrawal of the objection to the drawings.

Claim Rejections – 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1-4, 6-8, 10, 13, 27-37, and 168-172 stand rejected under 35 U.S.C § 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully traverse the rejection.

As a preliminary matter, Applicants respectfully submit that the claim scope has been misapprehended. The Office states that the claimed method "fairly encompasses … the use of an enzyme substrate as a label." (Office Action, p. 11). Applicants respectfully disagree. As amended, independent claim 1 is directed to method for detecting for the presence of antibiotic resistant *Staphylococcus* bacteria from total unamplified *Staphylococcus* genomic DNA in a sample using capture oligonucleotides bound to an addressable substrate and detector oligonucleotides bound to a gold

nanoparticle. Thus, the claimed methods do not encompass the use of an enzyme substrate as a label. The use of gold nanoparticles as detectable labels for target nucleic acids is described throughout the specification and the examples. Thus, the claims are commensurate in scope with the description in the specification.

The Disclosure Contemplates Alternative Detection Methodologies

The Office alleges that the specification does not enable the full scope of the claims. Specifically, at page 8 of the Office Action, the Examiner states:

> [I]t is noted with particularity that applicant was only able to achieve a detectable result when a specific signal amplification step was performed. The claimed method does not recite such a limitation.
> …
> A review of the disclosure fails to find where applicant contemplated alternative test conditions and detection methodologies, much less describe such alternative embodiments so as to reasonably suggest that they had possession of the full genus of methods encompassed the [t]he claims.

(Office Action, pp. 7-8). The Office points to a passage in the specification that states that the nanoparticles could not be visualized with the naked eye, and that the visualization was enhanced using signal amplification with silver (Specification, p. 58).

Applicants respectfully submit that the claims have been misapprehended. Neither the claim itself nor the specification limit the detecting to use of the naked eye. The detecting could occur by any means. Applicants respectfully direct the Examiner's attention to claims 13, 27-37 and pp. 29-31 of the specification in which alternative detection methods are described. Simply because the nanoparticles in Example 4 could not be visualized by the naked eye without signal amplification does not mean that unamplified nanoparticles could not be visualized using any of the other means described in the specification.

The specification states that various optical or flatbed scanners could be used to detect the nanoparticles. It also contemplates that a computer could be used to analyze or enhance the images obtained from a scanner. For instance, "the sensitivity of the assays can be increased by subtracting the color that represents a negative result from the color that represents a positive result." (Specification, p. 30, lines 17-18). This does not necessarily require signal amplification.

The substrate may also be placed between two electrodes to allow for the detection of conductive nanoparticles. The specification states that one could detect the nanoparticles by detecting a change in conductivity, which clearly does not require either optics or the naked eye (Specification, p. 31, line 20). Thus, it is clear from the specification that the use of a silver stain for signal amplification is an optional addition to the methods (Specification, p. 31, lines 1-12).

Further, Applicants respectfully remind the Office that the presence in inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled (MPEP 2164.08(b)). The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. (*See Id.*). The specification describes a variety of detection methodologies such that the full scope of the instant claims may be practiced by the skilled artisan without undue experimentation. It is within the realm of routine experimentation to determine whether a signal could be detected from the nanoparticles in the absence of silver enhancement. For at least this reason, the present ground of rejection should be withdrawn.

B. *The Specification Teaches How the Claimed Methods Overcome Problems in the Prior Art.*

The Office states that prior, as well as post-filing art, teaches numerous problems confronting those of ordinary skill in the art, and that these problems have not been addressed by the instant disclosure (Office Action, p.8). Specifically, the Examiner states that:

> A review of the instant disclosure fails to identify how these art-recognized issues are to be overcome such that the full scope of the invention can be practiced without the public having to resort to undue experimentation.

(Office Action, p. 12). Applicants respectfully disagree. Applicants have shown that the use of gold nanoparticles as detection agents provides significant advantages and allows for the detection of specific sequences in a complex background of nucleic acids. According to the specification,

> [N]anoparticle probes, particularly gold nanoparticle probes are surprising and unexpectedly suited for direct SNP detection with genomic DNA and without amplification. First, the extremely sharp melting transitions observed in nanoparticle oligonucleotide detection probes translate to a surprising and unprecedented assay specificity that could allow single base discrimination even in a human genomic DNA background.

(Specification, p. 29, lines 6-11, emphasis added). The specification also provides guidance on the specific hybridization conditions that could be used. As described in Example 2, the hybridization temperature for the assays may be very close to the T_m for the capture probes, and this "unexpectedly achieved an efficient hybridization, especially in the case where the target sequence represents only a minute fraction (*i.e.* 1/100,000,000 or a 1 million's %) of the complex DNA mixture that the human genome represents." (Specification, p. 48).

Applicants respectfully submit that provided only routine experimentation is needed to identify appropriate hybridization conditions and thus, practice the methods recited herein. Accordingly, Applicants respectfully request that the present ground of rejection of claim 1, and any claims depending therefrom, be withdrawn.

Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Respectfully submitted,

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